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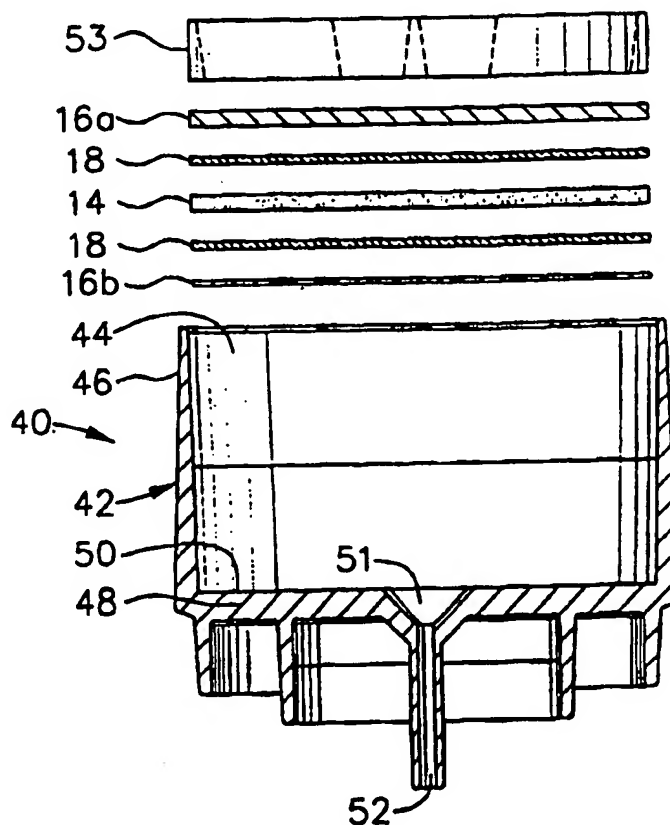
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(54) Title: MICROCOLUMN FOR EXTRACTION OF ANALYTES FROM LIQUIDS

(57) Abstract

An apparatus (10) for extracting an analyte from a liquid sample, comprises a microcolumn (12) having a microparticulate media therein, the media being sandwiched between two compression layers (18a, 18b). Preferably, the compression layers comprise a binder-free glass fiber, held in the microcolumn by upper and lower polypropylene mesh (16a, 16b). Preferably the microcolumn has a flat bottom (50) with a centrally located exit (51).



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**MICROCOLUMN FOR EXTRACTION OF ANALYTES  
FROM LIQUIDS**

**RELATED APPLICATION**

5           This application is a continuation-in-part of  
U.S. Patent Application Serial No. 08/275,781 filed July  
15, 1994, which is incorporated herein by reference.

**BACKGROUND**

10           The present invention relates to microcolumns  
for extraction of an analyte from a liquid sample, and  
particularly extraction of an analyte from biological  
fluids.

          Accurate and inexpensive detection of analytes  
15   present in liquid samples, for example in biological  
fluids, such as blood and urine, is important to health  
care. Tests for analytes in blood and urine are  
conducted to monitor the health of patients, detect the  
presence of disease conditions, and monitor for the use  
20   of illegal or restricted drugs. For example, doctors,  
when administering drugs such as antiarrythmics,  
asthmatic drugs, insulin, and anticoagulants, check the  
drug content of the blood to regulate the dosages of the  
patient. Drugs that can be abused, such as heroin,  
25   marijuana, cocaine, and codeine, can be tested to  
determine abuse of the drug, such as by employees and by  
athletes.

          A technique used for detection of analytes  
includes selectively extracting the analyte from the  
30   biological fluid onto a solid media. The analyte is then  
removed from the solid media by a suitable elution  
liquid, and tests are conducted to determine whether the  
analyte is present in the eluent liquid, such as by gas  
or liquid chromatography.

35           Prior art extraction columns have been  
effectively used. For example, it is known to use  
particulate silica as the solid media in a column. In

addition, silica has been provided embedded within an inert matrix of polytetrafluoroethylene ("PTFE") in the form of an extraction disk, which can be preloaded in a plastic barrel.

5           A problem with use of PTFE to hold the silica is that PTFE is hydrophobic and can require pre-conditioning with alcohol and high pressure so that the aqueous sample can flow therethrough. This increases the time and manpower required for the analysis.

10           Although these prior art devices can be effective, it is desirable to improve on these devices. It is desirable that the extraction device be fast, remove a high percentage of the analyte from the sample, be transportable, storable without damage, and be  
15 inexpensive. Moreover, it is desirable that any such device be compatible with existing automated equipment, and not leach into the biological fluid or the eluent liquid, any compound that could interfere with the analytical results.

20           Moreover, it is desirable to minimize the volume of biological fluid and wash eluent liquid. By minimizing the liquid volume, a more concentrated sample is obtained for analysis, the sensitivity of the test is enhanced, and less biological fluid needs to be obtained  
25 from the subject. High yields from the biological fluid with minimum elution volumes can be obtained by maintaining uniform flow through the extraction media, with no channeling and no dead volume.

30

#### SUMMARY

The present invention is directed to an extraction apparatus that meets these needs. The apparatus is useful for extracting a substance (also referred to as an analyte) from a liquid sample. The  
35 apparatus comprises a container, typically a microcolumn, having an entrance, an opposed exit, and a passage therebetween for passage of a liquid sample containing an

analyte therethrough. Within the passage is a thin layer of a microparticulate extraction media, typically silica particles. The media is selected for extracting the analyte from the liquid sample. The extraction media has a small particle size of less than 20 microns, which is provided in a very thin layer, so that the ratio of the effective diameter of the extraction media layer to the thickness of the layer is at least 5, and preferably at least 10.

10           The extraction media is sandwiched between upper and lower compression layers, which compress the silica extraction media therebetween. The compression layers are sufficiently porous that the liquid sample can flow therethrough, and are formed from a flexible, hydrophilic material. This is in contrast to the prior art preformed disks, which are made of polytetrafluoroethylene, which is hydrophobic, and thus slows down the flow of sample through the extraction media and utilizes preconditioning. The compression layer has a pore size less than the particle size of the extraction media, and is preferably formed of a spongy, glass fiber, having no binder.

25           Preferably the microcolumn also includes an upper mesh flow distributor above the upper compression layer, and a lower mesh flow distributor below the lower compression layer, sandwiching the compression layers and the layer of extraction media therebetween. The flow distributors hold the extraction media and the compression layers in the microcolumn and help distribute flow of the liquid sample to avoid channeling.

30           In a preferred version of the invention, the bottom of the container is substantially flat, with the exit substantially centrally located in the bottom. This ensures uniform flow of the liquid sample through the container.

35           Due to the combination of the very thin layer of extraction media and the compression layers, rapid

extraction of an analyte from a biological fluid can be obtained, with very small volumes of biological fluid, i.e., less than 0.5 ml, and only very small samples of elution liquid are needed, on the order of 0.5 to 0.75 ml. In addition, the extraction device of the present invention is inexpensive to use and manufacture, is stable during storage and transportation, and is compatible with existing automated equipment.

10

#### DRAWINGS

These and other features, aspects, and advantages of the present invention can be better understood with reference to the following description, appended claims, and accompanying drawings, where:

15

FIG. 1 is a perspective view of one version of a microcolumn according to the present invention;

FIG. 2 is a side elevation view, exploded, partly in section, of region 2 of the microcolumn of FIG. 1;

20

FIG. 3 is a side elevation view, partly in section, of the microcolumn of FIG. 1 in region 2 of FIG. 1;

25

FIG. 4 is a side elevation view, partly in section, of a different version of a microcolumn according to the present invention; and

FIG. 5 is a top plan view of the microcolumn of FIG. 4.

#### DESCRIPTION

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An apparatus 10 for extracting an analyte from a liquid sample is shown in FIGS. 1-3. The apparatus 10 comprises a microcolumn 12, which serves as a container for an extraction sandwich system. The extraction system is comprised of a five-layer sandwich construction, that includes (i) a thin extraction layer 14 of microparticulate solid extraction medium, (ii) an upper flow distributor 16a, (iii) a lower flow distributor 16b,

35

and two compression layers, (iv) an upper compression layer 18a between the upper flow distributor 16a and the extraction layer 14, and (v) a lower compression layer 18b between the lower flow distributor 16b and the extraction layer 14.

The microcolumn 12 has generally a tubular configuration, and has an entrance 20, an opposed exit 22, and a passage 23 therebetween for generally vertical flow. The flow can be effected with a vacuum system (not shown) or gravity alone. The passage 23, which is also referred to as a central bore, contains the extraction system. The exit 22 is preferably in the form of a luer-lock, which allows the apparatus 10 to be used with conventional automated extraction apparatus, such as a vacuum extraction apparatus, which are designed to receive an extraction column having a luer-lock.

A liquid sample flows in the direction of arrow 26 shown in FIG. 2 through the passage 23.

The portion of the microcolumn 12 above the extraction sandwich system serves as a reservoir for the liquid sample, from which an analyte is to be extracted, and also a reservoir for an eluent liquid.

All of the components of the apparatus 10 are made of materials that are substantially inert to biological fluids so that when blood or urine is passed through the apparatus 10, substantially nothing passes from the apparatus 10 into the blood or urine. Preferably, the microcolumn 12 is made of polypropylene, or alternatively, a fluorinated polymer.

A typical microcolumn according to the present invention has an internal diameter of about 1/4 to 1 inch, and a length, excluding the luer tip, of about 2 to about 6 inches.

The microcolumn 12 need not have the shape shown in the figures. For example, it need not be cylindrical in horizontal cross-section. In addition, in one embodiment of the invention, the entrance 20 can be

designed to receive a luer-lock extension so that a reservoir containing a liquid sample can be piggybacked on top of the microcolumn 12.

The extraction media 14 is formed of silica, such as a silica gel, constituted pure glass, modified silica, or polymeric resin such as divinyl benzene. The media particles are of small particle size, preferably having a number average of particle size of less than 20 microns, and more preferably, less than 10 microns. A suitable silica extraction media is described in U.S. Patent No. 4,650,714, which is incorporated herein by reference. A preferred microparticulate silica extraction media is available from J.T. Baker Chemical Company of Phillipsburg, New Jersey, and is sold under their catalog number 7049-01.

Because of the small particle size of the silica, and because it is not impregnated into a hydrophobic layer such as polytetrafluoroethylene, it is possible to have a very thin extraction layer. Typically, the thickness of the extraction layer is less than 1 mm, and typically from about 0.1 to about 0.8 mm. Preferably, the ratio of the effective diameter of the extraction layer to the thickness of the extraction layer is at least 5, more preferably at least 10, and most preferably at least 15. By "effective diameter" there is meant:

$$D_{eq} = (4A/\pi)^{1/2}$$

where  $D_{eq}$  is the equivalent diameter and A is the cross-sectional surface area of the bore of the microcolumn 12.

Preferably, the silica extraction media is placed in the microcolumn 12 using a slurry packing technique, utilizing as the carrier isopropanol.

The chief purpose of the compression layers 18 is to hold the extraction media in place and compressed as a thin extraction layer. Accordingly, the compression



layers 18 have a pore size less than the particle size of the silica extraction media. They are sufficiently porous that the liquid sample can flow therethrough, and are composed of a flexible, hydrophilic material.

5 Preferably the compression layers 18 are resilient or "spongy" to hold the microparticles in place. A preferred pore size for the compression layers is less than 5 microns, and more preferably less than 3 microns. The compression layers 18 generally are of the same  
10 thickness, having a thickness typically of from about 1/4 to about 1 mm, and preferably about 1/2 mm.

A suitable compression layer comprises a glass microfiber media made of analytically clean material. Suitable materials, which are available from Whatman  
15 Specialty Products, Inc. of Fairfield, New Jersey, include a borosilicate glass fibers that are analytically clean and include no binder. This material, when purchased, has a smooth side and a rough side, where the smooth side is of lower porosity than the rough side.  
20 Preferably, it is the smooth side that is placed in contact with the microparticles of the extraction layer 14.

The flow distributors 16, which are formed of a flexible mesh material, help provide uniform flow of the  
25 sample through the column, and physically retain the compression layers and microparticulate material in place in the column. Preferably, the mesh is 200 mesh or smaller (i.e., has a mesh number of 200 or higher). It is made of polypropylene, or alternatively,  
30 polytetrafluoroethylene. A suitable material is available from Tetko, Inc. of Briarcliff Manor, New York, under catalog number 5-420134.

As shown in FIG. 3, the lower flow distributor 16b seats against the sloped bottom portion of the  
35 microcolumn. The upper flow distributor 16a is sized so that it is held in the bore of the microcolumn 12 by a compression fit.

As described, the apparatus 10 is easy and inexpensive to manufacture, is transportable, and efficiently and effectively removes analytes from liquid samples, requiring only small amounts of the liquid sample and small amounts of eluent fluid. The microcolumn can easily be injected molded.

FIG. 4 shows an apparatus 40 that is substantially the same as the apparatus 10 of FIG. 1, except the configuration of container 42 of apparatus 40 is different from the configuration of container 12 of FIG. 1. In particular, apparatus 40 uses the same type of extraction layer 14, upper and lower flow distributors 16a and 16b, and upper and lower compression layers 18a and 18b as does apparatus 10. The container 42 has an open entrance or top 44, a peripheral side wall 46, and a bottom 48. The peripheral side wall 46 is generally circular in horizontal section. The internal wall or surface 50 of the bottom 48 is substantially flat, and is substantially perpendicular to the vertical fluid flow path through the apparatus 40. There is an exit hole 51 through the bottom 48 that communicates with an exit passage 52. A liquid sample is poured through the top of entrance 44, and passes through exit hole 51 and through passage 52. The exit hole 51 and passage 52 are substantially centrally located in the middle of the bottom 48. Preferably the exit hole 51 is the configuration of an inverted truncated cone, to direct liquid flow into the passage 52.

The flow pattern, as a result of the flat inner surface 50 and its centrally located exit 51, is axially located through the extraction layer 14 without channeling, i.e., substantially the entire microparticulate layer is used for extraction. This results in homogenous absorption of compounds of interest in the extraction layer 14, and efficient transmission of liquid through the system with minimum entrapment of liquid. Furthermore, in this design, due to the porosity

of the glass mat and the polypropylene screen flow distributors 16, the apparatus has low internal volume with minimal liquid retention. Minimum liquid retention reduces the amount of solvent used to remove any substances retained by the extraction medium. Thus, the apparatus 40 provides maximum extraction efficiency by the extraction medium, yet minimum solvent usage to reclaim the absorbed compounds of interest from the sorbent layer.

It is also an important feature of the present invention to select the internal diameter of the outlet passage 52 in order to create sufficient back pressure to facilitate uniform flow throughout the extraction layer 14. Typically  $D_e$  is 1 to 3 mm, for a  $D_c$  from 5 to 50 mm, where  $D_e$  is the internal diameter of the outlet passage 52, and  $D_c$  is the internal diameter of the main passage of the container 42.

The apparatus 40 also includes a top retaining ring 53, which has four radially inwardly projecting fingers 54. The retaining ring 53 fits into the container 42 and is held in place by a friction fit, with the fingers 54 holding the top flow distribution 16a in place.

Although the present invention has been described in considerable detail with reference to certain preferred versions thereof, other versions are possible. For example, the apparatus 10 is not limited to use with biological fluids, but can be used, for example, for testing ground water, drinking water, and other liquids for contaminants.

In addition, the extraction media does not have to be homogenous, but rather a different extraction media can be used in a single bed, or the apparatus can include multiple beds of extraction media for extracting different analytes from samples.

Therefore, the spirit and scope of the appended claims should not be limited to the description of the preferred versions contained herein.

## WHAT IS CLAIMED IS:

1. Apparatus for extracting a substance from a liquid sample comprising:
- 5           a) a container having an entrance, an exit, and a passage therebetween for passage of a liquid sample containing a substance to be extracted therethrough;
- b) within the passage, a thin layer of microparticulate extraction media for extracting the
- 10           substance from the liquid sample, wherein:
- (i) the extraction media layer has a top surface, a bottom surface, and a peripheral edge,
- (ii) the extraction media has a particle size of less than 20 microns,
- 15           (iii) the ratio of the effective diameter of the extraction media layer to the distance between its top and bottom surfaces is at least 5, and
- (iv) the extraction media layer is oriented in the passage so that liquid flows through the
- 20           extraction media layer from its top surface to the bottom surface; and
- c) an upper compression layer at the top surface of the extraction media layer and a lower compression layer at the lower surface of the extraction
- 25           media layer, the two compression layers pressing the extraction media therebetween, the compression layers being sufficiently porous that the liquid sample flows therethrough, the compression layers being formed of a flexible, hydrophilic, microfiber material and having a
- 30           pore size less than the particle size of the extraction media.

2. The apparatus of claim 1 wherein the apparatus is made of materials substantially inert to
- 35           biological fluids so that when blood or urine is passed through the apparatus, substantially nothing passes from the apparatus into the blood or urine.

3. The apparatus of claim 1 wherein the distance between the top and bottom surfaces of the layer of extraction media is less than 1 mm.

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4. The apparatus of claim 3 wherein the the distance between the top and bottom surfaces of the layer of extraction media is from 0.2 to 0.9 mm.

10

5. The apparatus of claim 1 wherein the compression layers are formed of the same material.

6. The apparatus of claim 1 including an upper mesh flow distributor above the upper compression layer  
15 for distributing flow of the liquid sample uniformly to the extraction media layer top surface.

7. The apparatus of claim 1 wherein the upper mesh flow distributor holds the compression layers and  
20 the extraction media layer in the container.

8. The apparatus of claim 1 including a lower mesh flow distributor below the lower compression layer.

25 9. The apparatus of claim 1 wherein the container has a bottom with the exit being in the bottom, the bottom having an internal wall, the internal wall being substantially flat.

30 10. The apparatus of claim 9 wherein the exit is substantially centrally located in the bottom.

11. The apparatus of claim 1 wherein the container includes an inner wall in contact with the  
35 peripheral edge of the media layer.

12. Apparatus for extracting an analyte from a liquid sample comprising:

- a) a microcolumn having an entrance, an opposed exit, and a passage for passage of the liquid sample downwardly therethrough;
- b) within the passage, a thin layer of microparticulate silica extraction media for the analyte, wherein:
  - (i) the extraction media layer has a top surface, a bottom surface, and a peripheral edge,
  - (ii) the extraction media has a particle size of less than 20 microns,
  - (iii) the ratio of the effective diameter of the extraction media layer to the thickness of the extraction media layer is at least 5, and
  - (iv) the extraction media layer is oriented in the passage so that liquid flows through the layer from its top surface to the bottom surface;
- c) an upper compression layer at the top surface of the extraction media layer and a lower compression layer at the lower surface of the extraction media layer, the compression layers pressing the silica extraction media therebetween, the compression layers being sufficiently porous that the liquid sample flows therethrough, the compression layers being formed of a flexible, hydrophilic, glass fiber and having a pore size less than the particle size of the silica extraction media;
- d) an upper mesh flow distributor above the upper compression layer for distributing flow of the liquid sample uniformly to the extraction media layer top surface; and
- e) a lower mesh flow distributor below the lower compression layer.

13. The apparatus of claim 12 wherein the pore size of the compression layer is less than 5 microns.

14. The apparatus of claim 12 wherein the microcolumn has a bottom with the exit being through the bottom, the bottom having an internal wall, the internal wall being substantially flat.

5

15. The apparatus of claim 14 wherein the exit is substantially centrally located in the bottom.

16. Apparatus for extracting an analyte from a liquid sample comprising:

10 a) a microcolumn having an entrance, an opposed exit, an inner peripheral wall, a substantially flat inner bottom wall, and a central bore therethrough for passage of a liquid sample containing an analyte therethrough, the exit being substantially centrally located in the bottom wall;

b) within the bore, a thin layer of microparticulate silica extraction media adapted for extracting the analyte from the liquid sample, the extraction media having a particle size of less than 20 microns, the extraction media having a top surface facing the entrance and a bottom surface facing the exit, the ratio of the diameter of the extraction media layer to the thickness of the layer being at least 10, the inner wall of the microcolumn being in contact with the peripheral edge of the extraction media layer;

c) an upper compression layer and a lower compression layer pressing the silica extraction media therebetween, the compression layers being sufficiently porous that the liquid sample flows therethrough and into the extraction media layer top surface and out of the extraction media layer bottom surface, the compression layers being formed of a flexible, hydrophilic, substantially binder free glass fiber and having a pore size less than the particle size of the silica extraction media; and



d) an upper mesh flow distributor above the upper compression layer and a lower mesh flow distributor below the lower compression layer sandwiching the compression layers and the layer of extraction media therebetween, the flow distributors holding the extraction media and the compression layers in the microcolumn, the upper compression layer distributing liquid sample uniformly across the top surface of the extraction media layer.

10

17. Apparatus for extracting an analyte from a liquid sample comprising:

a) a container having an entrance, an exit, and a passage therebetween for passage of a liquid sample containing an analyte therethrough, the container having a substantially flat bottom wall with the exit substantially centrally located therein;

b) within the passage, a thin layer of microparticulate extraction media for extracting the analyte from the liquid sample, wherein:

(i) the extraction media layer has a top surface, a bottom surface, and a peripheral edge,

(ii) the extraction media has a particle size of less than 20 microns,

(iii) the distance between the top and bottom surfaces of the extraction media layer is less than 1 mm, and

(iv) the extraction media layer is oriented in the passage so that liquid flows through the layer from its top surface to the bottom surface;

c) an upper compression layer at the top surface of the extraction media layer and a lower compression layer at the lower surface of the extraction media layer, the two compression layers pressing the extraction media therebetween, the compression layers being sufficiently porous that the liquid sample can flow therethrough, the compression layers being formed of a

flexible, hydrophilic, microfiber material and having a pore size less than the particle size of the extraction media;

5 d) an upper mesh flow distributor above the upper compression layer for distributing flow of the liquid sample uniformly to the extraction media layer top surface; and

e) a lower mesh flow distributor below the lower compression layer.

10

18. The apparatus of claim 17 including an upper mesh flow distributor above the upper compression layer for distributing flow of the liquid sample through the extraction media.

15

19. The apparatus of claim 18 wherein the upper mesh flow distributor holds the compression layers and the extraction media layer in the microcolumn.

20

20. The apparatus of claim 18 including a lower mesh flow distributor below the lower compression layer.

25 21. A method of extracting a substance from a liquid sample comprising the step of passing the liquid sample into the entrance of the apparatus of claim 1 for transverse flow through the extraction media layer and out the exit, wherein the substance is extracted from the liquid sample by the extraction media.

30

22. A method of extracting an analyte from a liquid sample comprising the step of passing the liquid sample into the entrance of the apparatus of claim 12 for transverse flow through the extraction media layer and  
35 out the exit, wherein the analyte is extracted from the liquid sample by the extraction media.

23. A method of extracting an analyte from a liquid sample comprising the step of passing the liquid sample into the entrance of the apparatus of claim 16 for transverse flow through the extraction media layer and out the exit, wherein the analyte is extracted from the liquid sample by the extraction media.

24. A method of extracting an analyte from a liquid sample comprising the step of passing the liquid sample into the entrance of the apparatus of claim 17 for transverse flow through the extraction media layer and out the exit, wherein the analyte is extracted from the liquid sample by the extraction media.

25. The apparatus of claim 1 wherein the ratio of the effective diameter of the extraction media layer to the distance between its top and bottom surfaces is at least 10.

26. Apparatus for extracting a substance from a liquid sample comprising:

(a) a container having a top, a bottom, an entrance in the top, an exit in the bottom, and a passage between the entrance and exit for downward passage of a liquid sample therethrough, the bottom having an inner wall which is substantially flat with the exit being substantially centrally located in the bottom; and

(b) within the passage, a thin layer of microparticulate extraction media for extraction of the substance from the liquid sample.

FIG. 1

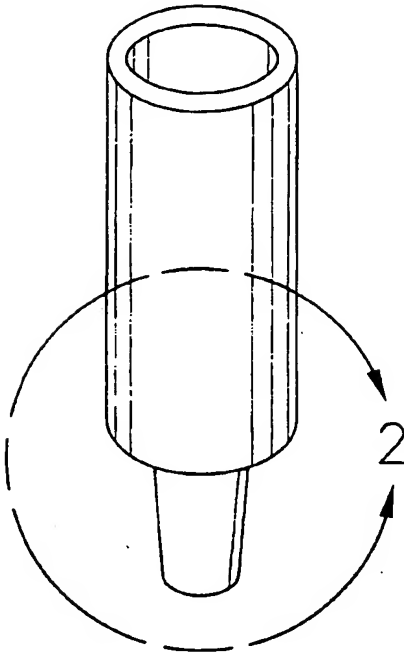


FIG. 2

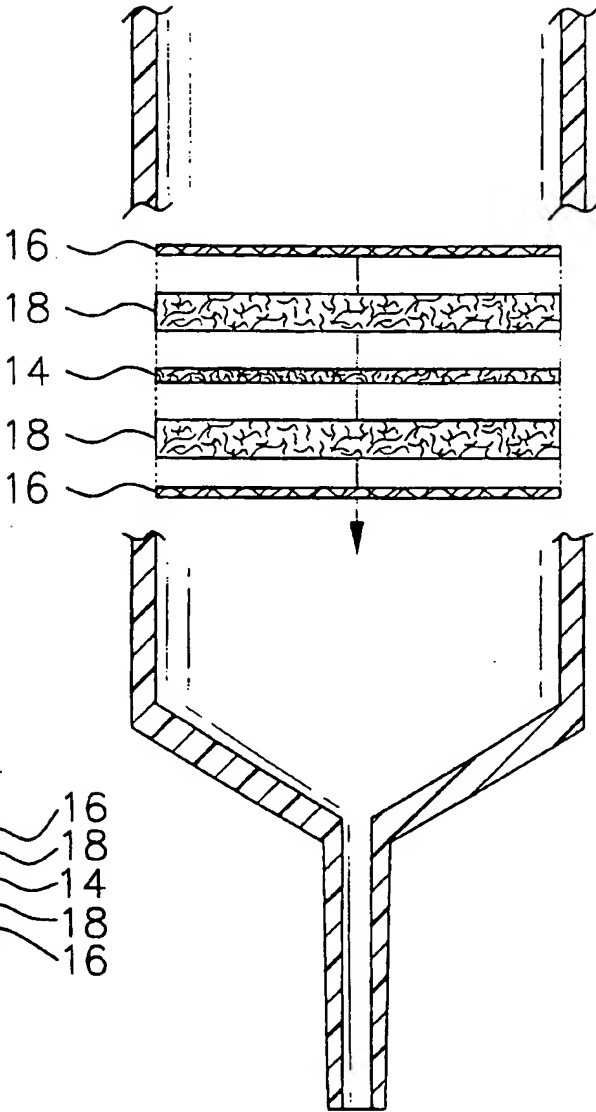
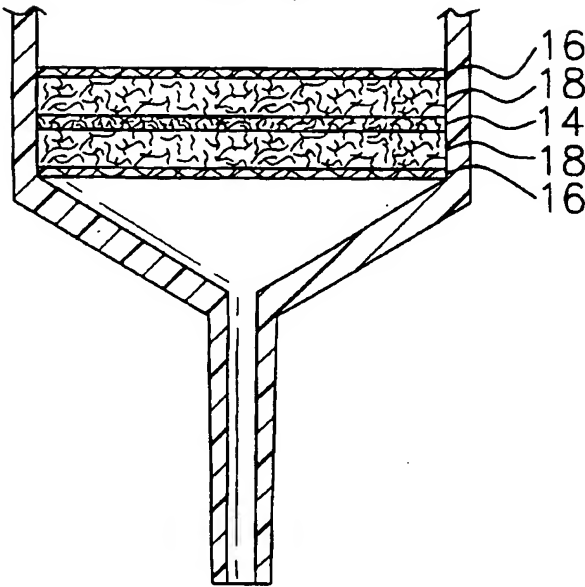


FIG. 3



# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US96/11300

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : B01D 24/00, 24/12, 24/22, 25/00, 29/085, 29/39, 37/00, 39/02

US CL : Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : Please See Extra Sheet.

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 4,774,058 A (E.L. MEHL) 27 SEPTEMBER 1988 (27.09.88), see entire document.	1-5, 9-11, 13-15, 21-22, 26
Y	US 5,318,703 A (R.B. HEILIGMAN) 07 JUNE 1994 (07.06.94), see entire document.	6-8, 12, 16-20
Y	US 5,279,742 A (C.G. MARKELL ET AL) 18 JANUARY 1994 (18.01.94), see entire document.	1, 12, 16, 17
X	US 5,391,298 A (R.M. PIEPER ET AL) 21 FEBRUARY 1995 (21.02.95), see entire document.	26
Y		1-4, 9-11, 12, 14-17, 20-25

☒ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

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\*T\*

later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

\*X\*

document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

\*Y\*

document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

\*Z\*

document member of the same patent family

Date of the actual completion of the international search

12 SEPTEMBER 1996

Date of mailing of the international search report

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## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US96/11300

## C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,433,847 A (R.G. RICE) 18 JULY 1995 (18.07.95), see entire document.	1-26

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US96/11300

## A. CLASSIFICATION OF SUBJECT MATTER:

US CL :

210/198.2, 263, 283, 287, 289, 290, 291, 435, 446, 456, 483, 484, 488, 489, 490, 491, 502.1, 503, 505; 422/58, 59, 60, 69, 70, 101, 102, 104; 436/177, 178, 527; 530/412, 413, 416, 417; 502/401, 405

## B. FIELDS SEARCHED

Minimum documentation searched

Classification System: U.S.

210/198.2, 263, 283, 287, 289, 290, 291, 435, 446, 456, 483, 484, 488, 489, 490, 491, 502.1, 503, 505; 422/58, 59, 60, 69, 70, 101, 102, 104; 436/177, 178, 527; 530/412, 413, 416, 417; 502/401, 405